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SPECIFICATION

Pharmaceutical preparations in retard form

The invention relates to a novel retard form of pharmaceutical preparation in which a core containing the active substance is provided with a semi-permeable diffusion coating, and to a process for the preparation thereof.

Methods of retarding the release rate of pharmaceuticals have been described in numerous publications; a survey of the most important principles is given, for example, in German Patent Specification No. 1 467 781. Pharmaceutical preparations adapted for slow release of active substance are sometimes described as being in retard or depot form.

The ideal oral depot form acts like a permanent intravenous infusion, i.e. it maintains (after a rapid increase to the desired level initially) a level of active substances in the blood which is as constant as possible for the desired duration of activity of the medicament (a so-called "plateau").

In practice various factors make it difficult to approach this ideal with preparations to be taken orally due to the varying conditions encountered during passage through the gastro-intestinal tract (differing from intravenous administration). Thus, for example, the pH-gradient, the motility and the enzyme content as well as the electrolytic properties and water content of the gastro-intestinal tract vary widely.

In order to obtain a constant release of active substance (reaction of zero order, the Soliva and Speiser, Pharmaceutica Acta Helvetiae *41,* 176-191 (1966)) there has been used more and more the idea of covering cores containing active substances with semi-permeable diffusion coatings. However, in this way alone, a rate of release of active substance free from exterior influences, especially from the pH variation in the gastro-intestinal tract, cannot be attained. The solubility of substances having pK_a values which are in the pH range of the stomach (1-3) or of the intestines (5-8) often vary considerably in this range and hence there is a variation in the rate of diffusion of active substance through the barrier formed by the coating.

An attempt has been made to solve this problem by developing an individually adjusted coating for each active substance. However, such a procedure results in considerable development work and cost.

It has also been proposed to obtain a pH-independent constant release rate without adapting the coating individually by mixing the active substance with buffer salts in the form of smaller particles, which particles are covered with materials that are film-forming so as to allow for diffusion of gastric and intestinal fluids, but which do not dissolve in these fluids (see German Offenlegungsschrift 24 14 868). However, trials have shown, that in this way only initially is the release rate pH-independent. Thus the pH-independence lasts for only a limited period of time; afterwards the original pH-dependence is again quickly exhibited.

According to the present invention it has now been found that depot forms of pharmaceutical preparations having a semi-permeable diffusion coating can be prepared so as to exhibit a substantially pH-independent release rate over the whole period of activity of the active substances therein if the coating is applied so as to consist of 20 to 90% by weight of ethyl cellulose and 10 to 80% by weight of a polyethylene glycol.

Thus, according to one feature of the present invention there is provided a pharmaceutical preparation in soluble dosage unit form having a sustained release of active substance and an improved constancy of rate of release of active substance in an environment of varying pH in the physiological range, which preparation comprises a core containing at least one active substance in association with a carrier or excipient, the said core being provided with a semi-permeable diffusion coating comprising from 20 to 90% by weight of ethyl cellulose and from 10 to 80% by weight of a polyethylene glycol.

The term "pH in the physiological range" as used herein means the range of pH encountered in the gastro-intestinal tract.

The term "soluble dosage unit" as herein means that the dosage unit does not contain a disintegrant.

According to a further feature of the present invention there is provided a process for the preparation of a pharmaceutical preparation in retard form as hereinbefore defined which comprises forming a core containing the active substance and coating the said core whereby a semi-permeable diffusion coating comprising from 20 to 90% by weight of ethyl cellulose and from 10 to 80% by weight of polyethylene glycol is applied. The production of a regular coating is affected amongst other things by the expansion and disintegration characteristics of the core, the mixture of solvents used to apply the coating and, of course, the thickness of the coating. In particular, for uniform permeability, it is desirable to apply the coating using a very high spray rate, to maintain the water content of the aqueous spray solution used to apply the coating constant and to heat the propellant.

Furthermore, it is preferred, when cores in the form of tablets are employed, to prepare them as so-called non-disintegrating tablets.

A further useful measure, even a necessary one for some active substances (in particular those which are basic and relatively insoluble), is the adjustment of the pH inside the coating i.e. in the core, so as to be acidic. It is especially useful to adjust the pH within the coating by incorporating acidic compounds which serve to provide a controlled disintegration rate. Thus it has been shown that by controlling the disintegration rate using acidic tablet excipients, depending on the penetration capacity and solubility of the active substance concerned, the release of basic active substances into the intestinal fluid may be made almost pH-independent over nearly the total period of function of the retard form. Particular acidic compounds which may be considered are, for example, organic food acids, such as e.g. citric acid and tartaric acid.

Retardation of the rate of disintegration provided by the acid additive may be accomplished by a

number of methods, for example, by microencapsulation or by coating finely crystalline substances with varying thicknesses of insoluble film-forming substances such as ethyl cellulose or insoluble Eudragit type compounds (polymeric lacquer substances based on acrylate or methacrylate), or by using polyactide (anhydride of lactic acid) or malic acid (relatively insoluble in aqueous medium). A further possibility is to convert the active substance itself (often only weakly basic) into an acidic salt by reaction with a strong acid, the salt giving an acidic reaction in an aqueous medium.

With certain active substances such as for example dipyridamol, it is particularly advantageous to react the active substances with an acidic compound such as tartaric acid or citric acid. Thus for example, tartaric or citric acid in an up to three molar quantity with dipyridamol forms a composition having relatively good solubility (1 g/ml) in water. However, on addition of too much water – for example 5 parts by weight/1.5-6 parts tartaric acid/2 ml water – a syrupy transparent mass forms which hardens spontaneously on standing hence giving rise to problems during granulation. Thus, for example, when producing dipyridamol-containing compositions for granulation with the aid of suitable acidic compounds, the quantity of liquid incorporated into the composition must be carefully controlled to avoid the addition of too much water i.e. to ensure smooth running of the granulation process.

In order to obtain a linear release pattern, it is important, furthermore, that a determined maximum core volume V_c is not exceeded. This volume, which depends on the relative solubility of the active substance S_{rel} (= soluble quantity . dose) as well as on the percentage of the dose X_L which is released linearly, may be calculated according to the following equation:

$$V_c = \frac{100 - X_L}{100 \,.\, S_{rel}}$$

As the criterion as to whether there is a release of zero order, the proportion of the periods of time required for a 90% and 50% release of active substance ($t_{90\%}/t_{50\%}$) may be used. For a reaction of zero order this value is 1.8; for a reaction of first order 3.3 and for a reaction of second order 9.0.

A further improvement in the release pattern of the pharmacutical preparations according to the invention having an acid-containing core may be obtained by adding to the diffusion coating, in addition to the ethyl cellulose and polyethylene glycol, up to 70% by weight of an acid-insoluble polymer i.e. one which is elutable only above pH 6. Acid-insoluble polymers which may be used for this purpose include for example, cellulose acetate phthalate (CAP), hydroxypropylmethyl cellulose phthalate (HPCP) and partially esterified polymethacrylic acid to which a softening agent is optionally added.

Pharmaceutical preparations in retard form according to the present invention which exhibit pH-independent release of active substance can be produced wherever the active substance is in high concentration. They may be administered individually or alternatively combined into larger retard units either with further retard forms, which may be the same or different, and/or with active ingredients in unretarded form. Thus, for example, an unretarded form may be placed with several retard forms possessing semi-permeable diffusion-coatings of increasing impermeability (caused by increasing thickness or varying composition of the coating) together into one gelatine capsule. In this manner the initial dose is provided by the unretarded form, the level being maintained with time by the retard forms having various release rates.

Such retard units are especially suited for cases where, due to the large relative solubility of the active substance S_{rel}, the volume of core V_c cannot be decreased correspondingly, or if the release of acid in the core cannot be adjusted exactly with the release of active substance. For active substances with decreasing resorbability during passage through the gastro-intestinal tract or if a resorption in portions is desired, this special type provides good results.

The following non-limiting examples serve to illustrate the present invention.

Example 1: Etilefrine Preparations

The sympathicomimetic 1 - (3 - hydroxyphenyl) - 2 - ethylamino - ethan - 1 - ol, known under the non-systematic name Etilefrine, is generally used in a dosage of from 5-100 mg and is an extremely water-soluble substance (approx. 660 mg/ml at 25° at a pH of from 1-8). It is therapeutically desirable for Etilefrine to have reached a high plasma level about 2 hours after administration, the level then slowly decreasing over a total period of 8 hours.

Example 1a: Etilefrine Retard Form

The tablet cores are produced in the usual way by mixing the active substance with conventional excipients such as lactose, polyvinyl pyrrolidone and a food colour. The mixture obtained is moistened, granulated and pressed into arcuate cores of approx. 5 mm diameter. (production of so-called "non-disintegrating tablets" without addition of disintegrant).

A number of cores, each containing 8 mg of active substance, are covered with a coating, which will disintegrate rapidly in an aqueous medium, consisting of hydroxypropylmethyl cellulose (90%) and polyethylene glycol (10%). The coated core is then dried to yield initial tablets.

In addition, there are produced per initial tablet prepared above four retard tablets. Each retard tablet contains 4.25 mg of active substance and is covered, using a conventional spray pistol, with a spray solution composed as follows:

ethyl cellulose N 14	6 parts
polyethylene glycol 6000	4 parts
ethanol (denaturated 0.3 % H_2O	45 parts
methylene chloride	45 parts

To half these retard tablets 4 mg of lacquer each are applied to give step 1 retard tablets whilst the other half is applied 8 mg of lacquer each to provide step 2 retard tablets. Both groups of filmed retard tablets are dried.

As a last step each initial tablet is encapsulated

together with two step 1 retard tablets and two step 2 retard tablets in a hard gelatine capsule by means of a filling device to give the final retard unit.

A single administration of this retard unit provides an equivalent therapeutic effect to that obtained by administering three times the quantity of Etilefrine tablets over an interval of 1.5 hours. Thus, using the retard unit, dosaging is essentially simplified for the physician. In addition, reduced side-effects occur (for example tachycardia) and the intensity of action is on the whole greater.

Retard unit of a combination Etilefrine/DHEMS. The retard unit is also particularly suitable for the production of combination preparations of Etilefrine with, for example dihydroergotamine. With such a preparation treatment of the so-called orthostase-syndrome may be carried out. As the dose of the dihydroergotamine may be much lower with such a preparation than that of the Etilefrine (0.5-10 mg compared to 5-100 mg) and as this active substance, in the form conventionally used which is the methanesulfonate, is much less soluble than Etilefrine, such a combination form may be prepared merely by adding to the above described Etilefrine retard unit a further initial tablet containing the active substance dihydroergotamine methanesulfonate (DHEMS).

The cores are produced in the same manner as indicated for the single preparation. In addition to the 5 Etilefrine cores, one of which contains 8 mg and the other four of which contain 4.25 mg of active substance, a further core is produced containing 2.5 mg of dihydroergotamine methanesulfonate (DHEMS).

Coating of the cores is also carried out in the manner indicated for the single preparation, the core containing the DHEMS being coated in the same way as the Etilefrine initial tablet. Coating of the retard tablets as well as filling of the finished tablets into capsules is carried out analogously to the single preparation, capsules being used which can take up a total of 6 tablets of 5 mm diameter.

Example 1 b

Etilefrine tablet cores (so-called "non-disintegrating tablets" without disintegrant), produced in the usual way by moist granulation and pressing, of approx. 5 mm diameter and 50 mg weight were coated, by means of a conventional spray pistol, with a spray solution composed as follows (indicated as parts by weight:

ethyl cellulose N14 (= content of ethoxyl 47.5-49 % viscosity 14 cps)	7 parts
polyethylene glycol (Polywax 6000), the word 'Polywax' being a registered Trade Mark) (average MG = 6000)	3 parts
ethanol, denatured (approx. 0.6 % water)	45 parts
methylene chloride	45 parts

In doing so, the following conditions were kept constant:

size of boiler
quantity of coating
batch size
spray device
spray distance
duration of drying
spray rate
water content of solvent
temperature of propellant

Example 1 c: Etilefrine Preparation

1. Core

a)	Etilefrine	20.0 mg
b)	tartatic acid (size of particles 0.3-0.6 mm in normal logarithmic distribution	25.0 mg
c)	lactose	59.7 mg
d)	magnesium stearate	0.3 mg
		105.0 mg

Constituents (a) and (b) are granulated moist and the granulate obtained is dried then mixed with constituents (c) and (d). The resultant mixture is pressed into tablet cores.

2. Coating

In a coating pan with air drying the tablet cores are sprayed with a 5% solution of ethyl cellulose (4 parts), polyethylene glycol, mol weight 5000-7000 (1 part), triacetine (0.4 parts) and cellulose acetate phthalate (4.6 parts) in an aqueous mixture from ethanol and methylene chloride, until a polymer quantity of 12 mg/tablet core has been applied.

Example 2: Clonidine Retard Form

The antihypertonic 2 - (2, 6 - dichlorophenylamino) - Δ - 2 - imidazoline, known under the non-systematic name Clonidine, is a salt form (for example HCl salt) of an intensely water soluble substance. It is therapeutically desirable for Clonidine to be administered over a period of 24 hours in such a way, that the highest plasma level is reached after 4 hours and is maintained up to the 10th hour at least,whereupon it then decreases slowly up to the 24th hour.

Tablet cores are produced in the usual way by mixing the active substance with conventional excipients such as lactose, polyvinyl pyrrolidone and a food colour e.g. food orange 2. The resultant mixture is granulated moist and then the homogeneous mixture thus obtained is pressed into arcuate cores of approx. 5 mm diameter. (production of so-called "non-disintegrating tablets" without addition of disintegrant). For the initial tablet is produced a core containing 50 mcg of active substance and it is covered with a coating, which disintegrates rapidly in an aqueous medium, consisting of hydroxypropylmethyl cellulose (90%) and polyethylene glycol (10%). The coated initial tablets are then dried.

Four retard tablets are produced per initial tablet each tablet containing 4.25 mg of active substance and being covered, by means of a conventional spray pistol, with a spray solution composed as follows:

ethyl cellulose N 14	5 parts
polyethylene glycol 6000	5 parts
ethanol (denatured 0.3 % H_2O)	45 parts
methylene chloride	45 parts

For step 1 retard tablets 5 mg of lacquer per tablet are applied whilst for step 2 retard tablets double the quantity of lacquer i.e. 10 mg is applied per tablet. The step 2 retard tablets are additionally coated with a coloured suspension, which gives a soluble coating. The filmed retard tablets are then dried.

As a last step each initial tablet is encapsulated together with two step 1 retard tablets and two step 2 retard tablets in a hard gelatine capsule by means of a filling device. Using this retard unit, the frequency of administration may be reduced as compared with the Clonidine forms presently on the market due to the considerable prolongation of the duration of activity as well as a reduction or avoidance of frequency and intensity of side effects (e.g. dryness of mouth). This applies to doses not only in the indicated range of 250 mcg but also to higher doses of 450 or 500 mcg. However, the retard form may be administered in the total range of doses from 0.1-1.5 mg with favourable result.

This retard unit is also especially suitable for the production of combination preparations of Clonidine with other blood-pressure decreasing active substances, for example with chlorothalidone or hydrochlorothiazide. With such a preparation the desired dose of the second active substance is generally higher than that of the Clonidine (10-50 mg compared with 0.05-1.5 mg). Therefore, such preparations may be prepared merely by adding to the Clonidine retard unit described above a further initial tablet containing the second active substance.

Retard unit of a Combination Clonidine/Chlorothalidone. The cores are produced in the same manner as indicated for the single preparation. In addition to the 5 Clonidine cores, one containing 50 mcg and the other four 4.25 mg of active substance, a further core is produced containing 15 mg of chlorothalidone.

Coating is carried out in the manner indicated for the single preparation, the core containing the chlorothalidone being coated in the same way as the Clonidine initial tablet. Coating of the retard tablets as well as filling of the finished tablets into capsules is carried out analogously to the single preparation, capsules being used which can take up a total of 6 tablets of 5 mm diameter.

Example 3: Fenoterol Retard Form

The broncholytically and tocolytically active 1 - (3, 5 - dihydroxyphenyl) - 1 - hydroxy - 2 - [(4 - hydroxyphenyl) - isopropyl - amino] - ethane known under the non-systematic name Fenoterol is a salt form and is very water soluble as the hydrobromide with a very short half life-time (22 min.). The conventional dosage range is from 2,5 to 30 mg.

The tablet cores are produced in the usual way by mixing the active substance with conventional excipients such as lactose, polyvinyl pyrrolidone and a food colour, granulating the mixture obtained moistened and pressing the resultant homogeneous mixture into arcuate cores of approx. 5 mm diameter. (production of so-called "non-disintegrating tablets" without addition of disintegrant). For the initial tablet is produced a core containing 2.2 mg of active substance which is covered with a coating, which disintegrates rapidly in an aqueous medium, formed from hydroxypropylmethyl cellulose (90%) and polyethylene glycol (10%). After coating the tablets are dried.

In addition, retard tablets are prepared, the cores of which each contain 1.6 mg of active substance. The cores are covered by means of a conventional spray pistol with a spray solution composed as follows:

ethyl cellulose N 14	5 parts
polyethylene glycol 6000	5 parts
ethanol (denatured, 0.3 % water)	45 parts
methylene chloride	45 parts

For step 1 retard tablets 9 mg of lacquer are applied to each core whilst for step 2 retard tablets 12 mg are applied. Afterwards, the filmed retard tablets are dried.

As a last step each initial tablet is encapsuled for example, with 3 retard tablets into hard gelatine capsules by means of a filling device.

With the retard unit described above a quick increase in the plasma level followed by a plateau lasting from 1.5 to 5.5 hours after administration may be obtained. Thus, in a single administration, an effect equivalent to the administration of two conventional Fenoterol tablets each containing 2.5 mg of active ingredient is attained without the need to administer tablets several times and at the same time avoiding large deviations in the plasma level. This is especially important for tocolytic administration of Fenoterol. According to the latest research for the best results a continuous treatment of the uterus-receptors must be attained.

In particular, the retard form is suitable for the production of combination preparations of Fenoterol with, for example, the active substance ipratropium bromide (= 8R - 8 - isopropyl - 3α - [± tropoyloxy] - 1αH, 5αH - tropanium bromide) of use in the treatment of diseases where air-passages become blocked. For this second active substance the dose is generally required to be higher in a preparation than that of Fenoterol (7.5-50 compared to 3.5-30). A suitable form may be obtained by addition to the above-described Fenoterol retard form of a further initial tablet containing the active substance ipratropium bromide, as follows:

Retard Form of a combined Fenoterol/Ipraptropium Bromide preparation.

The Fenoterol cores are produced in the same manner as indicated above for the single preparation, however, with half the quantity of active substance. In addition to the 4 Fenoterol cores, one containing 1.1 mg and three containing 0.8 mg each of active substance, a further core is produced containing 7.5 mg of ipratropium bromide. To produce this further core the active substance is granulated together with the excipients lactose, corn starch and magnesium stearate and the granulate obtained pressed into cores. Each core is then coated with an

aqueous film, for example containing 30% polyethylene glycol, 20% talcum, 5% TiO_2, an appropriate quantity of a food-colour lacquer and 40% hydroxypropylmethyl cellulose.

The coatings for the Fenoterol cores are produced in the manner indicated for the single preparation. Coating of the retard tablet as well as filling of the finished tablets into capsules is carried out as described for the single preparation, using capsules which can take up to 5 tablets with a 5 mm diameter.

Example 4: Mexiletine Retard Form

The anti-arrhythmic 1 - (2, 6 - dimethylphenoxy) - 2 - aminopropane, known under the non-systematic name Mexiletine, is a salt form (for example a HCl salt) which is well soluble in water. With Mexiletine it is therapeutically desirable to obtain a slow increase of the plasma level with a prolonged plateau formation. The conventional dose is from 0.1 to 1.5 mg.

The tablet cores are produced in the usual way by mixing the active substance with conventional excipients such as lactose, polyvinyl pyrrolidone and magnesium stearate, granulating the mixture obtained moist and pressing the resultant homogeneous mixture into arcuate cores of approx. 6.2 mm diameter. (Production of so-called "non-disintegrating tablets" without addition of disintegrant). Retard tablets of the same (moderate) retardation rate are prepared each containing 72 mg of active substance and being covered by means of a conventional spray pistol, with a spray solution composed as follows:

ethyl cellulose N 14	6 parts
polyethylene glycol 6000	4 parts
ethanol (denatured, 0.3 % water)	45 parts
methylene chloride	45 parts

Approx. 6 mg of lacquer is applied to each tablet and the filmed tablets are then dried.

As a last step the retard tablets are encapsulated into hard gelatine capsules by means of a filling device, six retard tablets being contained in each capsule.

The above example described a mexiletine form, leading to an optimal release curve in the above sense (slow increase with prolonged plateau formation) and, in addition, to a decrease in the main side effects (vertigo, nausea). Due to the longer duration of action, dosaging and administration is simplified.

Example 5: Bunitrolol Retard Form

The β-adrenolytic 1 - (2 - cyanophenoxy) - 3 - tert.butylamino - propan - 2 - ol, known under the non-systematic name Bunitrolol, is a well water-soluble substance in salt form (for example as hydrochloride). The conventional dose range is from 10-150 mg.

The tablet cores are produced in the usual way by mixing the active substance with conventional excipients such as lactose, polyvinyl pyrrolidone and a food colour, granulating the resultant mixture moist and pressing of the homogeneous mixture thus obtained into arcuate cores of approx. 5 mm diameter. (production of so-called "non-disintegrating tablets" without addition of disintegrant). For the initial tablet a core is produced containing 10 mg of active substance which is then covered with a coating which disintegrates rapidly in an aqueous medium, consisting of hydroxypropylmethyl cellulose (90%) and polyethylene glycol (10%). The tablets are then dried.

In addition are produced per initial tablet two retard tablets, each containing 10 mg of active substance and being covered by means of a conventional spray pistol, with a spray solution composed as follows:

ethyl cellulose N 14	5 parts
polyethylene glycol 6000	5 parts
ethanol (denaturated 0.3 % H_2O)	45 parts
methylene chloride	45 parts

6 mg of lacquer are applied to each retard tablet which is then dried.

As a last step each initial tablet is encapsulated with two retard tablets in a hard gelatine capsule by means of a filling device.

Using this retard form a quick increase of the plasma level may be obtained with prolonged plateau formation. The dosage delivery thus obtained simplifies the administration process of the β-adrenolytic and reduces the danger of an involuntary over-dosaging, which is a danger with β-adrenolytics. Furthermore the side effects (based upon plasma tops) such as too strong a decrease of blood pressure or strong bradycardia are decreased.

The retard form is also suitable for the production of combination preparations of Bunitrolol with, for example antihypertonics such as hydrochlorothiazide and/or Triamterene, or blood-vessel dilating agents such as isosorbide dinitrate.

The dose of the above-mentioned antihypertonic is generally, in such a preparation, 5-50 mg or 10-50 mg. (Bunitrolol: 10-150 mg, preferably 30 mg). In a combined preparation with isosorbide dinitrate a dose of 10-150 mg. preferably 30 mg of isosorbide dinitrate would in general be appropriate. For such preparations it is sufficient to add to the above Bunitrolol retard form one or more initial tablets containing the additional active substances, as shown in the following:

Retard Form of a Combination Bunitrolol/Hydrochlorothiazide/Triamterene

The Bunitrolol cores are produced in the same manner as indicated above. In addition to the 3 Bunitrolol cores each containing 10 mg of active substance is produced a further core containing 12.5 mg of Hydrochlorothiazide as well as one containing 25 mg of Triamterene, these latter cores being prepared by mixing the active substance together with lactose, corn starch and magnesium stearate and food-colour and pressing the same.

The coatings are produced as indicated for the single preparation, the cores containing the additional active substances being coated in the same way as the Bunitrolol initial tablets. Coating of the Bunitrolol retard tablets as well as filling of the finished tablets into capsules is effected as described for the single preparation, using capsules which can incorporate a total of 5 tablets with 5 mm diameter.

Example 6: Codeine phosphate Retard Form

The analgesic Codeine is a substance which is moderately water soluble in salt form (for example as phosphate) and which is administered generally in a dosage range of from 15-150 mg, preferably 25-75 mg.

An optimal release curve for Codeine phosphate (gaining the highest plasma level after approx. 2 hours, then plateau formation with subsequent slow decrease over 8-10 hours) is reached with the depot form described in the following example:

The tablet cores are produced in the usual way by mixing the active substance with conventional excipients such as lactose, polyvinyl pyrrolidone and a food colour, granulating the mixture obtained moist and pressing of the resultant homogeneous mixture into arcuate cores of approx. 5 mm diameter. (production of so-called "non-disintegrating tablets" without addition of disintegrant). For the initial tablet is produced a core containing 20 mg of active substance which is then covered with a coating, which disintegrates rapidly in an aqueous medium, consisting of hydroxypropylmethyl cellulose (90%) and polyethylene glycol (10%). The coated core is then dried.

In addition, there are produced, per initial tablet, four retard tablets, each containing 10 mg of active substance and being covered by means of a conventional spray pistol, with a spray solution composed as follows:

ethyl cellulose N 14	5 parts
polyethylene glycol 6000	5 parts
ethanol (denaturated 0.3 % H_2O)	45 parts
methylene chloride	45 parts

6 mg of lacquer are applied to each core which is subsequently coated with a coloured suspension, giving a soluble coating and then dried.

As a last step each initial tablet is encapsulated with three retard tablets into a hard gelatine capsule by means of a filling device. One single administration of this retard form is approx. equivalent to a dose of 25 mg of unretarded Codeine phosphate administered twice within a period of three hours; however, the plasma level is essentially more constant. The retard form simplifies considerably the dose scheme for the physician and improves compatibility.

The retard form is also particularly suitable for the production of combination preparations of Codeine phosphate with, for example the analgetically active substance doxylamino succinate. In such preparations the doxylamino succinate dose is generally lower than that of the Codeine phosphate (5-50 mg compared to 10-150 mg). For such preparations it is sufficient to add to the above Codeine phosphate retard unit a further initial tablet containing the active substance doxylamino succinate, as described in the following.

Retard Form of a combined Codeine Phosphate/Doxylamino Succinate preparation

The cores are produced in the same manner as indicated for the single preparation. In addition to the 4 Codeine phosphate cores one of which contains 20 mg and the remaining three 10 mg of active substance, is produced a further core containing 10 mg of doxylamino succinate by granulating the active substance together with lactose, corn starch, colloidal silicic acid, soluble starch and magnesium stearate and pressing the same.

Coating is in the manner indicated for the single preparation, the core containing the doxylamino succinate being coated in the same manner as the Codeine phosphate initial tablet. Coating of the retard tablet as well as filling of the finished tablets into capsules is effected analogously to Example 1, using capsules that may incorporate 5 tablets of 5 mm diameter.

Example 7:

Retard form of 2 - amino - 6 - ethyl - 4, 5, 7, 8 - tetrahydro - 6H - oxazolo [5, 4d] azepine dihydrochloride

2 - amino - 6 - ethyl - 4, 5, 7, 8 - tetrahydro - 6H - oxazolo [5, 4d] azepine is a substance having a blood-pressure decreasing and antianginous effect and is well water soluble in salt form (for example as the dihydrochloride).

The tablet cores are produced in the usual way by mixing the active substance with conventional excipients such as lactose, polyvinyl pyrrolidone and a food colour, granulating the mixture obtained moist and pressing the resultant homogeneous mixture into arcuate cores of approx. 5 mm diameter (production of so-called "non-disintegrating tablets" without addition of disintegrant). For the initial tablet is produced a core containing 5 mg of active substance the core being covered with a coating, which disintegrates rapidly in an aqueous medium, consisting of hydroxypropylmethyl cellulose (90%) and polyethylene glycol (10%). The coated cores are dried.

In addition are produced per initial tablet three retard tablets, each containing 5 mg of active substance and being covered by means of a conventional spray pistol, with a spray solution composed as follows:

ethyl cellulose N 14	8 parts
polyethylene glycol 6000	2 parts
ethanol (denaturated 0.3 % H_2O)	45 parts
methylene chloride	45 parts

3 mg of lacquer are applied to each core and the filmed retard tablets are then dried.

The above procedure is carried out under anhydrous coniditions as the active substance is unstable in the presence of water.

As a last step each initial tablet is encapsulated with 2 retard tablets into a hard gelatine capsule by a filling device.

With this retard form it is possible to obtain a substantially constant plasma level and to suppress undesired side effects (for example a temporary too strong decrease of blood-pressure). Furthermore the dosage scheme for the physician is simplified.

Example 8:

Dihydroergotamino methanesulfonate (DHEMS)-preparation

1. Core

a) dihydroergotamino methane sulfonate	0.5 mg
b) lactose	26.9 mg
c) citric acid (particle size 0.3-0.6 mm in normal logarithmic distribution)	20.0 mg
d) ethyl cellulose	2.4 mg
e) magnesium stearate	0.2 mg
	50.0 mg

Constituent (c) is coated with constituent (d) in a fluid bed and constituent (a) is mixed with constituent (b) and granulated moist. After mixing the components together with constituent (e), the resultant mixture is pressed into tablets arcuate on both sides and of 5 mm diameter.

2. Coating

In a coating pan with air-drying, the tablets are sprayed with a 5% solution of ethyl cellulose (3 parts) and polyethylene glycol mol weight 5000-7000 (7 parts) in an aqueous mixture of ethanol/methylene chloride until a polymeric quantity of 6 mg per tablet core has been applied.

Example 9: Papaverine Preparation

1. Core

a) Papaverine	10.0 mg
b) lactose	18.6 mg
c) citric acid (particle size 0.3-0.6 mm in normal logarithmic distribution)	20.0 mg
d) ethyl cellulose	1.2 mg
e) magnesium stearate	0.2 mg
	50.0 mg

The core is produced as described in Example 8.

2. Coating

The coating is effected as described in Example 8, but using 4 parts of ethyl cellulose, 6 parts of polyethylene glycol (mol weight 5000-7000). This is applied up to a polymeric quantity of 9 mg per tablet core.

Example 10: Quinidine Sulfate Retard Form

The anti-arrhythmic Quinidine (mostly used as the sulfate) is a substance relatively insoluble in water. The dose range is generally from 150-1500 mg.

With such an active ingredient it is useful to produce all unretarded initial tablets in a readily disintegrable form (for example by addition of corn starch and/or microcrystalline cellulose). Furthermore it is important to add acid substances (e.g. organic food acids) to the retard tablets in order to improve the solubility of the active substance in the core.

The readily disintegrable initial tablets are produced by mixing the active substance with the excipients corn starch, polyvinyl pyrrolidone, colloidal silicic acid, microcrystalline cellulose and magnesium stearate, granulating the mixture obtained moist and pressing the resultant homogeneous mixture into arcuate cores of approx. 6.2 mm diameter. The cores of the retard tablets are prepared without corn starch, but citric acid is added. For the intial tablets (two per unit) cores with 50 mg of active substance are produced and coated with a coating, which disintegrates rapidly in aqueous medium, consisting of hydroxypropylmethyl cellulose (90%) and polyethylene glycol (10%). The coated cores are then dried.

In addition 4 retard tablets are prepared per unit, each containing 50 mg of active substance and being coated with a spray solution, applied by means of a conventional spray pistol, the solution being composed as follows.

ethyl cellulose N 14	6 parts
polyethylene glycol 6000	4 parts
ethanol (denaturated, 0.3 % water)	45 parts
methylene chloride	45 parts

To each retard tablet core is applied 5 mg of lacquer and the tablets are then dried.

As a last step two initial tablets are encapsulated together with four retard tablets into a hard gelatine capsule by means of a filling device.

The retard form again considerably simplifies the dosage scheme of the physician. Furthermore too high plasma levels which may easily occur leading to too strong an effect may be avoided which is of special importance for an antiarrhythmic.

The retard form is suitable for production of combination preparations of the quinidine with additional active substances, which substances may be incorporated as a further initial tablet.

Example 11: Dipyridamol Retard Form

The coronary therapeutic Dipyridamol, used as a base, is a substance relatively insoluble in water; it is generally used in a dose of 150-400 mg.

As core excipients for a retard form with pH-independent release, particularly suitable are acidic compounds which form with the active substance Dipyridamol in one to three molar amounts, very good water soluble (> 1 g/ml) complexes. Suitable acidic compounds include, for example, tartaric acid and citric acid. However, on addition of too much water, for example an amount of 5 parts by weight/1.5-6 parts by weight tartaric acid/2 ml water a syrupy transparent mass forms which spontaneously hardens on standing thus giving rise to problems during granulation. Therefore, when producing Dipyridamol granulates containing such acidic compounds, the quantity of liquid used in the granulation (e.g. water) must be carefully controlled to avoid addition of too much liquid, otherwise problems will occur during granulation.

Readily disintegrable initial tablets are produced by mixing the active substances with conventional excipients such as e.g. lactose and corn starch and granulating the mixture obtained moist. The resultant homogeneous mixture is pressed into arcuate cores of approx. 6.2 mm diameter. The cores of the retard tablets are made of lactose, tartaric acid 25 mg) and magnesium stearate. The initial tablet contains 25 mg of active substance and is coated with a coating, which disintegrates rapidly in an aqueous medium, consisting of hydroxypropylmethyl cellulose (90%) and polyethylene glycol (10%).

In addition are produced per initial tablet five

retard tablets (as non-disintegrating tablets). Each retard tablet core contains as well 25 mg of active substance, 25 mg of tartaric acid. The cores are coated, by means of a spray pistol, with a spray solution having the following composition:

ethyl cellulose N 14	4 parts
polyethylene glycol 6000	6 parts
ethanol (denaturated, 0.3 % water)	45 parts
methylene chloride	45 parts

To each retard tablet core is applied 6 mg of lacquer. The tablets are then dried.

As a last step one initial tablet is encapsuled with five retard tablets in a hard gelatine capsule by means of a filling device.

The retard form considerably simplifies the dosage scheme of the physician. Furthermore too high plasma levels leading to too strong an effect which can easily occur with conventional administration may be avoided, this being of special importance with a cardiac agent.

This retard form is also suitable for the production of combination preparations of Dipyridamol with, for example acetyl salicyclic acid, e.g. by incorporating the additional active substance into the gelatine capsule as further retard tablets.

Example 12: Dipyridamol Retard Form

Dipyridamol retard tablets cores were prepared as described in Example 11 and coated, analogously to Example 11, with a 5% by weight spray solution of:

ethyl cellulose N14	4 parts
Polyethylene glycol 6000	2 parts
cellulose acetate phthalate	3.6 parts
triacetin	0.4 parts

in an aqueous mixture of ethanol and methylene chloride. To each retard tablet core is applied 4 mg of lacquer.

Comments to the Examples

The release of active substances of the various formulations in artificial intestinal fluids was examined in the Sartorius disintegrating model, the word 'Sartorius' being a registered Trade Mark (Pharm. Ind. *33*, 446 (1971), *38*, 232, 289 (1976)). The following results were obtained:

a) Etilefrine (see Example 1b and 1c)

During the release of Etilefrine (pk_a values: 2.6; 8.8; 10) out of tablets which are covered with a semipermeable diffusion-coat, the pH value of the solvent (artificial stomach or intestinal fluid) does not show any influence on the release of active substance using the tablets without added acid addition as well as using tablets with coated and non-coated citric acid. This is because of the very good solubility of Etilefrine which is generally pH-independent. In all cores over the range of pH 1-pH 8 approx. 660 mg/ml will dissolve (25°C). By varying the composition of the coating, it has been shown that in an artificial intestinal fluid of pH 7 coatings of 100% ethyl cellulose are substantially impermeable whilst coatings of ethyl cellulose into which polyethylene glycol is incorporated show a release pattern which is substantially linear up to approx. 60%. This has proved to be true also for coatings with a portion of the acid-insoluble polymer hydroxypropylmethyl cellulose phthalate (HPCP), provided the tablet cores do not contain an acid.

On the other hand, however the rate of active substance release increases with time up to approx. 60%, with acid-containing tablets having coatings which include the acid-insoluble polymer CAP.

b) DHEMS (see Example 8)

The dihydroergotamine methanesulfonate (DHEMS, $pk_a = 6.7$) shows a completely different release-pattern from Etilefrine. From coated tablets without acid excipients a very slow release of active substance is effected in the pH-range of the intestines: pH 6.0 - pH 7.5. The pH-dependence and the low degree of release is a result of the solubility of DHEMS which amounts to approx. 2×10^{-1} mg/ml at pH 6.0 and 2×10^{-2} mg/ml at pH 7.3. The release rate may be increased by addition of acidic tablet excipients, such as for example citric acid. The pH-dependence however is not completely eliminated, as in this case the acid excipient diffuses out of the coated preparation more quickly than the active substance. Only by the partial coating of the acid tablet excipient, so as to lead to a retarded dissolution of the acid excipient in the interior of the coated form, may be pH-dependence of the DHEMS-release be substantially eliminated. The optimal degree of coating of the acid excipient depends a.o. upon the diffusion properties of the corresponding active substance: for DHEMS it amounts to approx. 12%. Too strong retardation of the dissolution of the acid reduces again the release of active substance.

c) Dipyridamol (see Example 12)

As a result of the strong pH-dependence of solubility of the active substance (pH 1: > 1000 mg/l, pH 6: 7 mg/l, pH 7: 1 mg/l) an extremely slow release is obtained at neutral pH, unless the tablets contain an acid excipient or unless the active substance is converted into an acid salt (for example Dipyridamol citrate).

Acid-containing tablets with a coating of ethyl cellulose and a water-soluble polymer release the active substance at a rate which corresponds to a 1st order reaction. If the tablet coating contains acid-insoluble polymers, the change of the release-rate tends to be inverse: the release rate increases with time. The release-rate may also be varied by the thickness of the coating, the rate being inversely proportional to the thickness.

d) Papaverine (see Example 9)

Similar to DHEMS, Papaverine is a weakly basic substance with a pk_a value of 6.4. Its solubility is stongly pH-dependent (appox. 318 mg/ml at pH 3.0, approx. 5.10^{-2} mg/ml at pH 6.0 and approx. 2.10^{-2} mg/ml at pH 7.3). Due to its low solubility in artificial intestinal fluid, the release-rate from tablets with a diffusion coating is extremely small. Just as in the case of DHEMS, the release-rate is strongly increased by the inclusion of acid tablet excipients (for example citric acid); the pH-dependence of the release however is only eliminated initially as with DHEMS.

A partial coating of the acid tablet excipient with an insoluble film-former, for example ethyl cellulose,

eliminates the pH-dependence. The optimal degree of coating does not only depend upon the diffusion properties of the active substance, but also upon the permeablity and thickness of the diffusion coating, as well as the type and distribution of particle-size of the acid excipient.

The optimum quantity for coating of Papaverine in the form of acid-containing tablets having 6.0 mg of a diffusion coating per tablet is approx. 12 mg of ethyl cellulose/100 mg citric acid. For corresponding tablets having 9.0 mg of diffusion coating per tablet, approx. 6 mg of ethyl cellulose/100 mg of citric acid is preferred. (Anhydrous, size of particles 0.3-0.6 mm in normal logarithmic distribution).

CLAIMS

1. A pharmaceutical preparation in soluble dosage unit form having a sustained release of active substance and an improved constancy of rate of release of active substance in an environment of varying pH in the physiological range, which preparation comprises a core containing at least one active substance in association with a carrier or excipient, the said core being provided with a semi-permeable diffusion coating comprising from 20 to 90% by weight of ethyl cellulose and from 10 to 80% by weight of a polyethylene glycol.

2. A pharmaceutical preparation as claimed in claim 1 wherein the permeability of the coating is substantially the same over its whole surface.

3. A pharmaceutical preparation as claimed in claim 1 or claim 2 wherein the core is in the form of a tablet.

4. A pharmaceutical preparation as claimed in any preceding claim wherein the core contains one or more acidic compounds.

5. A pharmaceutical preparation as claimed in claim 4 wherein the acidic compounds are organic food acids.

6. A pharmaceutical preparation as claimed in claim 4 or claim 5 wherein the acidic compounds are in a form in which their disintegration is retarded.

7. A pharmaceutical preparation as claimed in claim 6 wherein the disintegration rate of the acidic compounds is slower than that of the active substance.

8. A pharmaceutical preparation as claimed in claim 6 or claim 7 wherein the acidic compounds are coated with an insoluble film-forming agent.

9. A pharmaceutical preparation as claimed in claim 4 wherein the acidic compound and active substance together form a water-soluble core composition.

10. A pharmaceutical preparation as claimed in claim 4 wherein the active ingredient is in the form of an acidic salt.

11. A pharmaceutical preparation as claimed in any one of claims 4 to 10 wherein the coating additionally contains up to 70% by weight of an acid-insoluble polymer.

12. A pharmaceutical preparation as claimed in claim 11 wherein the acid-insoluble polymer comprises cellulose acetate phthalate.

13. A pharmaceutical preparation as claimed in any preceding claim wherein the core volume does not exceed a maximum volume V_c as calculated according to the equation:

$$V_c = \frac{100 - X_L}{100 \cdot S_{rel}}$$

where

X_L = percentage of dose released according to zero order

and

S_{rel} = soluble quantity/dose.

14. A pharmaceutical preparation as claimed in any preceding claim wherein the active substance comprises 1 - (3 - hydroxyphenyl) - 2 - ethyl - amino - ethan - 1 - ol, 2 - (2,6 - dichlorophenylamino) - Δ - 2 - imidazoline, 1 - (3,5 - dihydroxyphenyl) - 1 - hydroxy - 2 - [(4 - hydroxyphenyl) - isopropylamino] - ethane, 1 - (2,6 - dimethylphenoxy) - 2 - aminopropane, 1 - (2 - cyanophenoxy) - 3 - tert. butylamino - propan - 2 - ol, codeine, 2 - amino - 6 - ethyl - 4,5,7,8 - tetrahydro - 6H - oxazolo[5,4d] - azepine, dihydroergotamine, papaverine, quinidine, dipyridamol or a salt thereof.

15. A pharmaceutical preparation as claimed in claim 1 substantially as herein described.

16. A pharmaceutical preparation as claimed in claim 1 substantially as herein described in any one of Examples 1 to 11.

17. A pharmaceutical preparation in dosage unit form comprising one or more retard forms as claimed in any preceding claim.

18. A pharmaceutical preparation in dosage unit form as claimed in claim 17 wherein the active substance is present in both retarded and unretarded form.

19. A pharmaceutical preparation in dosage unit form as claimed in claim 17 or claim 18 wherein the active substance is present in two or more retard forms having different disintegration rates.

20. A pharmaceutical preparation in dosage unit form as claimed in any one of claims 17 to 19 containing a further active substance in unretarded form.

21. A pharmaceutical preparation in dosage unit form as claimed in any one of claims 17 to 20 in the form of a capsule.

22. A pharmaceutical preparation in dosage unit form as claimed in claim 17 substantially as herein described.

23. A pharmaceutical preparation in dosage unit form as claimed in claim 17 substantially as herein described in any one of Examples 1 to 11.

24. A process for the preparation of a pharmaceutical preparation as claimed in claim 1 which comprises forming a core containing the active substance and coating the said core whereby a semi-permeable diffusion coating comprising from 20 to 90% by weight of a water-insoluble film former and from 10 to 80% by weight of a water-soluble polymer is applied.

25. A process as claimed in claim 24 wherein the core contains one or more acidic compounds.

26. A process as claimed in claim 24 or claim 25 wherein the coating is applied to the core as an aqueous solution in the form of a spray at a high spray rate, the water content of the spray being maintained substantially constant during the application.

27. A process for the preparation of a pharmaceutical preparation as claimed in claim 1 substantially as herein described.

28. A process for the preparation of a pharmaceutical preparation as claimed in claim 1 substantially as herein described in any one of Examples 1 to 11.

29. Pharmaceutical preparations as claimed in claim 1 whenever prepared by a process as claimed in any one of claims 24 to 28.

30. Pharmaceutical preparations as claimed in claim 1 whenever prepared by a process as claimed in claim 26.

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